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Mosaicism for Deletion 1p36.33 in a Patient With Obesity and Hyperphagia

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We report on a 4-year-old girl with obesity and hyperphagia whose peripheral blood cytogenetic analysis showed mosaicism for a deletion of band 1p36.33. Terminal 1p deletions are rarely reported and this patient represents the first identified case of mosaicism. Given the subtlety of the cytogenetic abnormality and the possibility of mosaicism, the incidence of such deletions has probably been underestimated. While a characteristic phenotype associated with this karyotypic abnormality was described recently, the present report highlights the additional clinical findings of obesity and hyperphagia and the overlap of manifestations with Prader-Willi syndrome. Am. J. Med. Genet. 70:409–412, 1997.

KEY WORDS: mosaicism; 1p36.3 deletion; Prader-Willi syndrome; obesity; hyperphagia

INTRODUCTION

We describe a 4-year-old girl with hyperphagia and obesity and mosaicism for a deletion of the distal short arm of a chromosome 1, resulting in monosomy of band 1p36.33. Deletions of 1p36.3 were described recently in the literature to be associated with a characteristic phenotype [Reish et al., 1995]. The present report represents, to our knowledge, the first identified case of mosaicism for this deletion. Additionally, the present case highlights an association of obesity and hyperphagia with the 1p deletion syndrome.

CLINICAL REPORT

The patient was referred at 4 1/2 years to a pediatric endocrine clinic for evaluation of obesity. She was born to a healthy 25-year-old mother at 38 weeks of gestation with a birth weight of 2,780 gms. At 3 weeks she presented with seizures. The patient had severe developmental delay with little or no acquisition of language, strabismus, hearing loss, and hypotonia. Behavior problems included temper outbursts, impulsivity, and self-injurious behaviors (biting her hands when angry). The patient had a history of hyperphagia, which the mother attempted to control by placing a gate across the kitchen doorway at night. This problem had become progressively more severe with age, and the child's weight had increased from the 50th centile to well above the 95th centile (approximately 4 SD above the mean) within the last 2 years. Head MRI and CT scans were normal.

On physical examination, her height was 102 cm and weight was 25 kg. She had a narrow forehead, deep-set eyes, with "almond"-shaped palpebral fissures, flat mid face, and a small down-turned mouth with a high arched palate (Fig. 1). The ears were small (–1 SD) but well formed and normally placed. The hands were small primarily because of short fingers (midfinger as

Fig. 1. The patient at 4 7/12 years.

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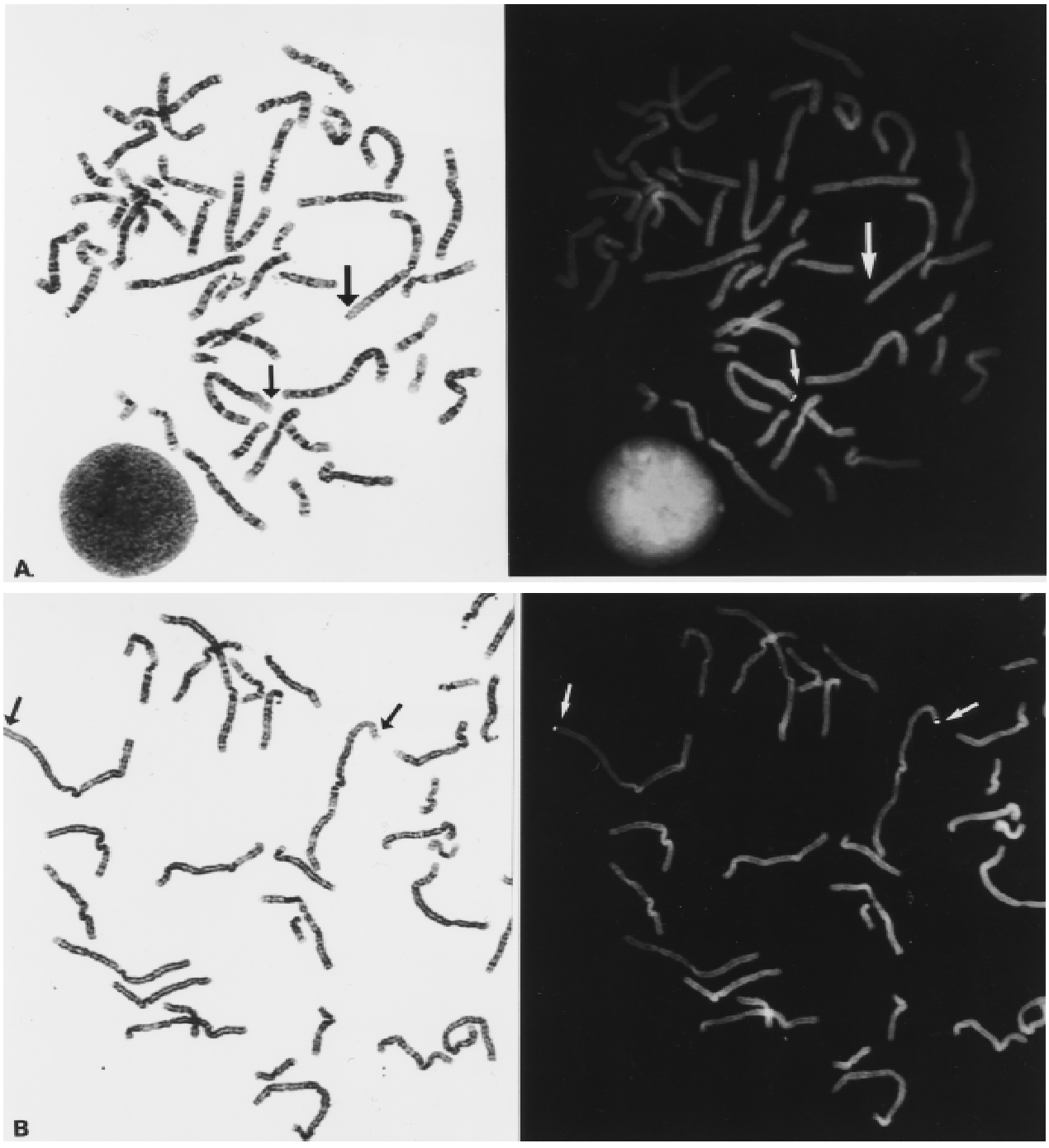

Fig. 2. **A:** G banding → FISH of a metaphase cell containing one normal 1 and one deleted 1. The larger arrow designates the deletion of band 1p36.33 detected by G-banding and the deletion of locus D1Z2 detected by FISH. **B:** G banding → FISH of a metaphase cell containing two normal 1 chromosomes. Band 1p36.33 is visible in both 1 homologues as is locus D1Z2.

% total hand length 35%), with 5th finger clinodactyly. The feet were small with short toes. On her initial evaluation, history and physical findings suggested the possible diagnosis of Prader-Willi syndrome as she was given a score of 6 using a weighted point system based on consensus diagnostic criteria for Prader-Willi syndrome [Holm et al., 1993].

CYTOGENETIC ANALYSIS

Twenty metaphase cells from peripheral blood were analyzed using high-resolution G-banding. Seven had a normal 46,XX female karyotype. The remaining 13 cells had a very small deletion of the distal short arm of one chromosome 1, involving band 1p36.33. An addi-

tional 50 metaphase cells were screened. Of these, 34 cells had the deletion and 16 did not.

FISH was performed using probe D1Z2 (Oncor, Gaithersburg, MD) containing midisatellite sequences from band 1p36.3. In 12 of 20 metaphase cells screened, hybridization was detected on only one 1 homologue, consistent with a deletion of this locus. In the remaining eight cells, hybridization was detected on both 1 homologues, consistent with the presence of two normal 1 chromosomes.

Sequential G-banding to FISH confirmed that those metaphases designated as normal by G-banding showed no deletion of D1Z2 by FISH, while those G-banded metaphases designated as having a deletion of 1p36.33 did show a deletion of D1Z2 by FISH (Fig. 2A,B). Because of the initial clinical diagnosis of Prader-Willi syndrome, FISH was also performed using probes for the SNRPN and D15S10 loci. No deletions of this region was detected. Thus, the karyotype of this patient is designated: mos46,XX,del(1)(p36.33).ish del(1)(p36.33)(D1Z2$^-$),15q11.2(D15S10 × 2, SNRPN × 2)[47]/46,XX.ish 1p36.3(D1Z2 × 2),15q11.2(D15S10 × 2, SNRPN × 2)[23].

DISCUSSION

Including the present case, a total of 18 cases of terminal 1p deletions is documented in the literature. The true incidence of obesity and hyperphagia among these patients is unknown. More than half were neonates or infants at the time they were reported, which would have been prior to the age when such a problem might manifest [Hain et al., 1980, Desangles et al., 1983, Steele et al., 1984, Barbi et al., 1992, Legare et al. ,1994, Keppler-Noreuil et al., 1995]. Of the remaining cases, two were institutionalized adults who did not have free access to food [Reish et al., 1995]. Among other patients reported during childhood, one had hyperphagia and obesity beginning at age 9 [Wenger et al., 1988], and two of the patients in our original series [Reish et al., 1995] subsequently developed this problem. Whether this has also occurred in the two additional patients reported in childhood [Pavlová et al., 1985, Gecnik and Genciková, 1987] is unknown.

The similarity between patients with a 1p deletion and those with Prader-Willi syndrome has been noted [Wenger et al., 1988]. Overlapping phenotypic characteristics include almond-shaped palpebral fissures, small hands and feet, small down-turned mouth, and structural abnormalities of the eyes. Mental retardation (although more severe in patients with 1p deletion) and behavior problems are also shared manifestations. Obesity and hyperphagia, long recognized to be cardinal manifestations of Prader-Willi syndrome [Holm et al., 1976; Cassidy, 1984], also appear to be problems that these disorders have in common.

Approximately 70% of patients with Prader-Willi syndrome have been found to have a deletion of 15q11.2 [Ledbetter et al., 1981; Butler et al., 1990]. Of the remainder, most have maternal uniparental disomy [Woodage et al., 1994]. Imprinting errors have also been identified in a small number of PWS patients [Reis et al., 1994]. Given the phenotypic similarities, it is possible that a proportion of patients with unexplained PWS may actually have a deletion of 1p36.3. The latter deletions are quite small and could easily be missed, depending on the level of G-banding resolution.

Although there are relatively few reported patients with 1p36.3 deletions, the subtlety of the abnormality may lead to an underestimation of its true incidence. Since the report of our series [Reish et al., 1995], we have identified three new cases. The observation that this deletion can also occur in mosaic form adds another level of complexity to its detection. However, the combination of high resolution G-banding analysis and FISH with the DIZ2 probe should facilitate the cytogenetic diagnosis.

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